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Setting Reactions and Compressive Strengths of Calcium Phosphate Cements

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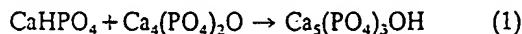
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Setting reactions and compressive strengths of a self-hardening calcium phosphate cement (CPC) were investigated. The CPC consists of tetracalcium phosphate (TTCP) and anhydrous dicalcium phosphate (DCPA). The cement specimens were prepared by mixing 0.7 g of the powder (TTCP 72.9 wt% + DCPA 27.1 wt%) with 0.175 mL of the liquid (25 mmol/L H₃PO₄ and 1.32 mmol/L sodium fluoride). The specimens were removed from the molds at pre-determined time intervals after being mixed, and their compressive strengths were measured. Immediately afterward, the fractured specimens were rapidly frozen in ethanol (-80°C), lyophilized, and examined by powder x-ray diffraction and scanning electron microscopy (SEM). The results showed that (1) hydroxyapatite was the only reaction product; (2) the reaction was nearly completed within four h, during which both the reaction product and compressive strength increased linearly with time, resulting in a strong correlation between the two; and (3) fully set CPC consisted primarily of small rod-like crystals and some platy crystals.

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Introduction.

A self-setting cement consisting of only calcium phosphate compounds was reported by Brown and Chow (1986). The major components of this calcium phosphate cement (CPC) are tetracalcium phosphate (TTCP), Ca₄(PO₄)₂O, and anhydrous dicalcium phosphate (DCPA), CaHPO₄, or dicalcium phosphate dihydrate (DCPD), CaHPO₄·2H₂O. These react in an aqueous environment to form, as the final product, hydroxyapatite (OHAp), Ca₅(PO₄)₃OH, the putative mineral in teeth and bones (Eq. 1).



Because of the apatitic nature of the set cement, it is highly compatible with soft and hard tissues (Gruninger *et al.*, 1984). The combination of setting and biocompatibility makes CPC a potentially useful material in a variety of dental and medical applications. These include the use of CPC as an endodontic filling material (Chohayeb *et al.*, 1987; Sugawara *et al.*, 1990),

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Certain commercial materials and equipment are identified in this paper to specify the experimental procedure. In no instance does such identification imply recommendation or endorsement by the National Institute of Standards and Technology or the ADA Health Foundation or that the material or equipment identified is necessarily the best available for the purpose.

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as an implant material for periodontal bone defects (Lu *et al.*, 1988), and as a binder for other non-setting calcium phosphate implant materials (Hanker *et al.*, 1987).

The objective of the present study was to obtain data on more fundamental physicochemical properties of CPC. In this study, the cement setting reaction of CPC consisting of TTCP and DCPA was investigated by powder x-ray diffraction, the compressive strengths of the set CPC specimens were measured as a function of time after the powder and liquid phases were mixed, and the morphology of the CPC was examined by scanning electron microscopy.

Materials and methods.

Preparation of CPC powder. — TTCP was prepared by heating an equimolar mixture of DCPA and CaCO₃ at 1500°C for 24 h, as described by Brown and Epstein (1965). The DCPA was a commercially obtained reagent-grade chemical. Results from preliminary experiments showed that CPC mixtures consisting of medium-particle-size TTCP and fine-particle-size DCPA produced stronger samples. Consequently, TTCP was pulverized in a blender (Micro Mill, Bel-art Products, Raritan, NJ) to obtain particle sizes about 1 to 10 μm. The DCPA was ground in distilled water for 48 h in a centrifugal ball mill (Model P6, International Equipment, Needham Heights, MA) to a median particle size of 0.3 to 4 μm. Fifty grams of the ground DCPA was then suspended in 500 mL of 25 mmol/L H₃PO₄ for 30 min (to remove possible hydrolysis products of DCPA formed during the grinding process) and then filtered. The cement components, dried and stored in a vacuum desiccator, were combined in the blender to obtain the desired composition.

Preparation of specimens. — The solid phase consisted of an equimolar mixture of TTCP and DCPA. The liquid phase was an aqueous solution of 25 mmol/L of H₃PO₄ and 1.32 mmol/L (25 ppm) of fluoride (F) from sodium fluoride (NaF). The F was included because results from preliminary experiments suggested that this level of F in the liquid facilitated reproducible setting. Since the F in the liquid would introduce a negligibly small amount of F (< 7 ppm) into the specimen, it was not expected to produce any significant effects on the overall composition of the cement. To prepare cement specimens, 0.7 g of CPC powder was mixed with 0.175 mL of the liquid phase so that the powder-to-liquid ratio (P/L) was 4.0 (wt/wt). In a preliminary study (Fukase *et al.*, 1989), this P/L ratio was found to be optimum for producing a paste of workable consistency. Samples also set with greater strength than those specimens produced with lower P/L ratios. After a mixing time of 30 s, the paste was loaded into a stainless steel mold (6 mm D × 12 mm H) by spatulation and with periodic packing by means of a stainless steel rod (5.6 mm D). The force applied to the rod during packing was limited to 2 kg, corresponding to a maximum pressure of 8.2 kg/cm². This was done by placing the mold on a digital scale and observing the reading while applying the force. The top and bottom surfaces of the mold were then covered tightly with two glass plates held by a "c"-clamp and stored in a 37°C, 100% humidity

box for 0.5, one, two, three, four, or 24 h. After the predetermined intervals, the hardened CPC specimens were removed from the molds for measurement of compressive strengths. At least five specimens were used for each selected interval.

Compressive-strength measurement.—The diameter and length of each specimen were first measured with a micrometer. The compressive strength was measured on a Universal Testing Machine (United Calibration Corp., Garden Grove, CA). The samples were placed between steel platens, which were covered with one thickness of wet filter paper, and tested at a loading rate of 1 mm/min.

Powder x-ray diffraction.—Following the compressive strength measurement, portions of the crushed pieces of the specimen were immediately placed in a tube containing ethanol (100%) cooled to -80°C and freeze-dried. In this way, the cement setting reactions would be stopped at the specific periods. The freeze-dried samples were ground to fine powders and were characterized by powder x-ray diffraction (XRD) to determine the extent of conversion of the starting materials and the identities of the products as a function of time. X-ray diffraction patterns were recorded on a Rigaku powder diffractometer with graphite-monochromatized copper $\text{K}_{\alpha 1}$ radiation ($\lambda = 0.154 \text{ nm}$) generated at 40 kV and 25 mA. All data were collected in a continuous scan mode ($0.5^{\circ} 2\theta/\text{min}$, time constant 2 s) on a strip-chart recorder. The relative peak intensities of the 013 and 040 reflections of TTCP at 29.2° and $29.8^{\circ} 2\theta$, respectively, were recorded a minimum of four times, averaged, and used to estimate the amount of starting cement ingredients present in the samples. These were the only major peaks of the reactants free of overlapping. An experimentally observed constancy in peak breadth ($\beta_{1/2} = 0.11^{\circ} 2\theta$)—and,

therefore, in the height/area ratio throughout the reaction—made it feasible to use peak heights rather than areas as numerical measures of changes in peak intensities. The extent of the cement setting reaction estimated from the TTCP intensity data, R_{TTCP} , was calculated by the following equation:

$$R_{\text{TTCP}} = [(T_0 - T_t) / (T_0 - T_e)] \times 100 \quad (2)$$

where T_0 is the sum of the 013 and 040 TTCP peak intensities in the original cement powder, T_t is the corresponding value in the specimen collected at time t (0.5, one, two, three, or four h) after mixing, and T_e is the trace residual TTCP peak intensity in the 24-hour specimen. As described later, there were trace amounts of residual TTCP present in most 24-hour specimens, and the term T_e was included in the equation to correct for this. The extent of the cement setting reaction was also determined, based on the OHAp peak intensity data, by means of the equation,

$$R_{\text{OHAp}} = (H_t / H_e) \times 100 \quad (3)$$

where H_t is the 002 ($2\theta = 25.9^{\circ}$) OHAp peak intensity in the specimen at time t , and H_e is the OHAp 002 peak intensity in the 24-hour specimens. However, overlap with adjacent TTCP peaks and changes in peak breadth with reaction time made this OHAp peak a less reliable measure of the setting reaction than the TTCP peaks.

Statistical analysis of data from compressive-strength and x-ray-diffraction measurements.—A least-squares procedure was used to evaluate the dependence of strength or the extent of

TABLE
EXTENT OF CPC SETTING REACTION AND COMPRESSIVE
STRENGTH AS A FUNCTION OF TIME

Time (hours)	Extent of Reaction		Compressive Strength (MPa)
	R_{TTCP}	R_{OHAp}	
0.5	8 (1)	—	10.7 (0.4)
1	32 (4)	—	17.0 (0.9)
2	59 (2)	55 (4)	30.7 (0.2)
3	82 (3)	70 (4)	31.8 (0.8)
4	97 (1)	88 (1)	36.7 (1.2)
24	100	100	36.0 (0.3)

$n = 5$; numbers in () denote standard errors.

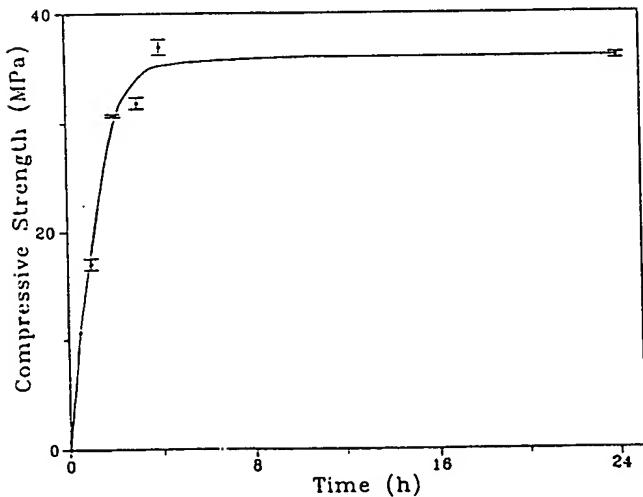


Fig. 1—Compressive strength as a function of time for the CPC specimens.

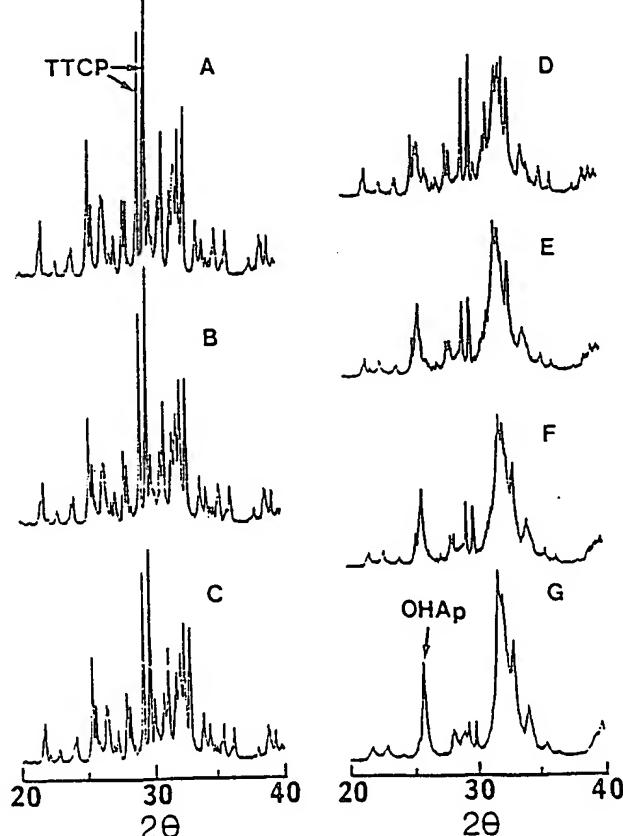


Fig. 2—XRD patterns of the CPC specimen at various intervals: (A) 0 h, (B) 0.5 h, (C) 1 h, (D) 2 h, (E) 3 h, (F) 4 h, and (G) 24 h. The peaks used for the calculation of the extent of reaction are marked as TTCP and OHAp.

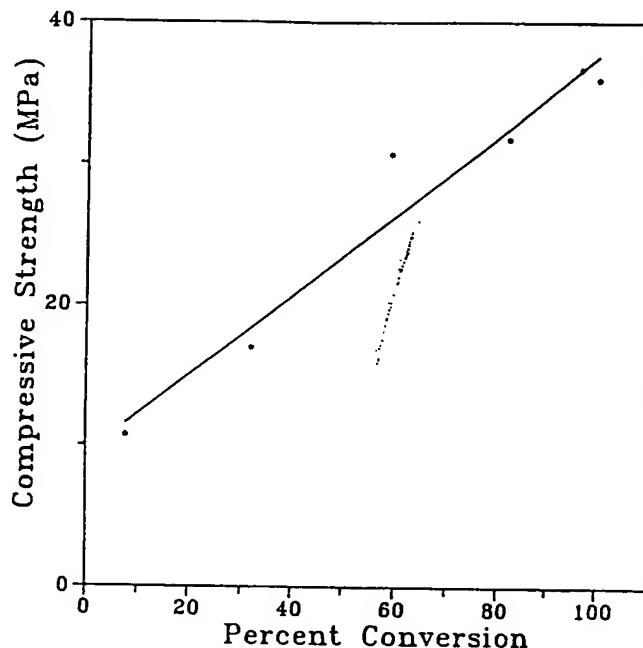


Fig. 3—Correlation between compressive strength and the extent of the cement setting reaction (R_{TTCP}). The correlation coefficient is 0.98.

setting reaction on time. The same method was also used to determine the correlation between compressive strength and the extent of reaction.

Scanning electron microscopy.—Several freeze-dried samples of the crushed specimens collected following the compressive-strength measurement described above were mounted on aluminum stubs and coated with gold-palladium. The SEM (model C-800, Hitachi) examinations were focused primarily on the fractured surfaces of the specimens. Micrographs with magnifications up to 100,000 of each of these areas were obtained.

Results.

Compressive strengths.—The compressive strengths of the CPC specimens as a function of time are shown in the Table and Fig. 1. For the initial four-hour period, the compressive strength of CPC increased approximately linearly with time ($R = 0.94$). The maximum compressive strength was obtained within four h after mixing. The compressive strength at 24 h was nearly the same as that at four h.

XRD patterns and extent of cement setting reaction.—The XRD patterns of specimens obtained at the various time intervals showed (Fig. 2) that the only reaction product present was OHAp. The extent of reaction, expressed in terms of R_{TTCP} and R_{OHAp} , as a function of time is given in the Table. As the reaction time increased, both the R_{TTCP} and R_{OHAp} values increased as expected. During the first four h after mixing, both R_{TTCP} and R_{OHAp} varied approximately linearly with time ($R = 0.98$ and 0.91, respectively). Although the maximum extent of CPC reaction was obtained in the 24-hour samples, the differences between the four- and 24-hour samples were relatively small. There were no discernible changes in the XRD patterns for any of the samples beyond 24 h. However, trace amounts of residual TTCP were present in most 24-hour specimens, probably because of a slight excess of it in the starting cement powder. Fig. 3 shows that the compressive strengths of CPC specimens were strongly correlated with the R_{TTCP} ($R = 0.98$).



Fig. 4—SEM photomicrograph of unreacted CPC powder. Bar = 10.0 μm .

SEM examination.—Shown in Fig. 4 is a typical micrograph of the original cement powder before mixing. The particles ranged from sub- μm to over 10 μm in size, consistent with the known range of particle sizes of the TTCP and DCPA. All particles appeared to be irregular in shape, probably a result of the ball milling and grinding processes used in reducing the particle size and in mixing the solids. The specimens obtained one h after the mixing showed (Fig. 5a) the outlines of the original particles and, in addition, the presence of some amorphous-looking materials in inter-particle spaces. Micrographs of higher magnifications (Fig. 5b) revealed that the "amorphous" materials consisted of small petal-like crystals. These appear to be the products of the cement setting reaction that may be responsible for causing the particles to adhere to one another. The two-hour specimens showed greater amounts of materials present in inter-particle spaces. The newly formed crystals were more rod-like, and fewer platy crystals were present. As the reaction time increased, the amount of the inter-particle materials became larger, and the crystallinity of these materials was higher. In the four-hour sample, the outlines of the initial particles became less apparent, and the crystals produced by the cement setting reaction became larger. In the 24-hour sample (Figs. 6a and 6b), the crystals present in areas adjacent to a void grew radially and were well-separated. In contrast, the crystals present in areas where there was a high density of materials were tightly packed, often arranged in a parallel manner. The cement specimens appeared rather amorphous-looking under low magnifications; however, under higher magnifications, it was apparent that the cement consisted of mostly crystalline materials.

Discussion.

Despite the high solid-to-solution ratio (4.0) in the cement pastes, the setting reaction was essentially completed in four h, with nearly all of the DCPA and TTCP converted to OHAp. This is quite intriguing because OHAp is known to form rather slowly and incompletely from hydrolysis of DCPA or DCPD

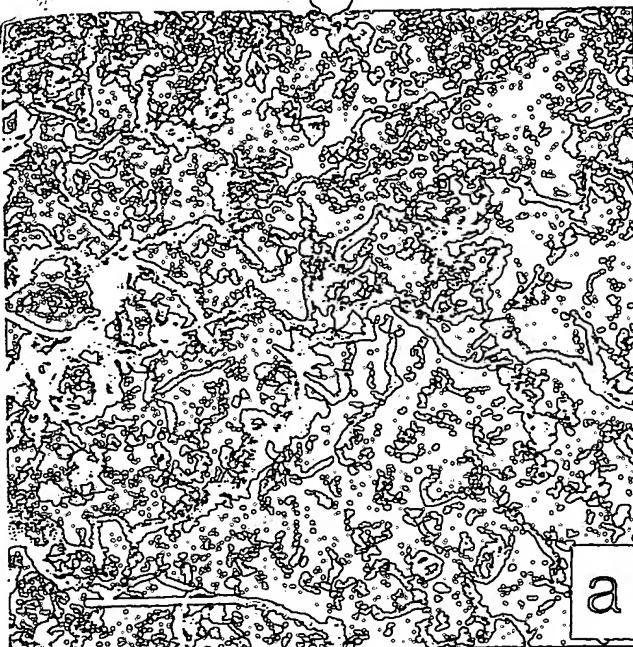


Fig. 5—SEM photomicrographs of the one-hour CPC specimen. (a) Bar = 10.0 μm ; (b) bar = 0.1 μm .

at neutral pH and in the absence of TTCP (Tung *et al.*, 1985). Based on the phase diagram of calcium phosphates in the three-component system (Brown and Chow, 1986), the liquid phase in the cement is also supersaturated with respect to octacalcium phosphate (OCP), $\text{Ca}_8\text{H}_2(\text{PO}_4)_6 \cdot 5\text{H}_2\text{O}$, and OCP can be expected to form because it is a more rapid-forming phase than OHAp (Brown, 1973). Although OCP was not detected by XRD in any of the samples in the present study, the appearance of a plate-like crystalline product suggests that transient formation of this phase may have occurred (Brown *et al.*, 1987).

During the first four h, the cement setting reaction proceeded at a near-constant rate, indicating that it may have followed zero-order reaction kinetics. This would suggest that the re-

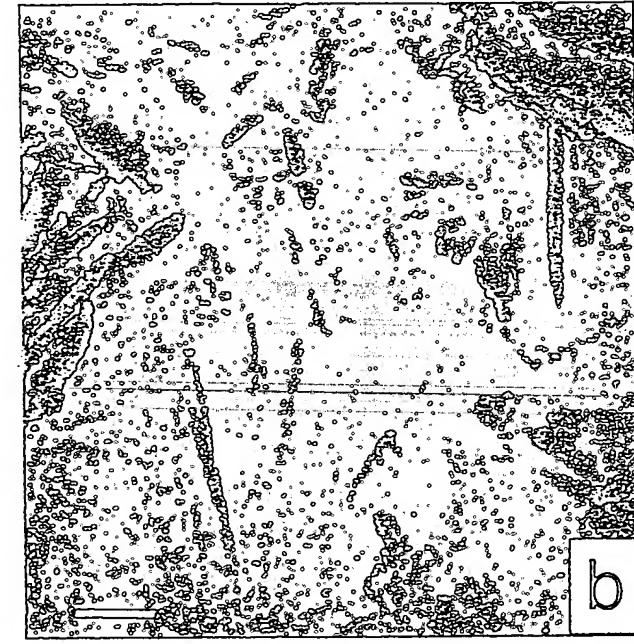
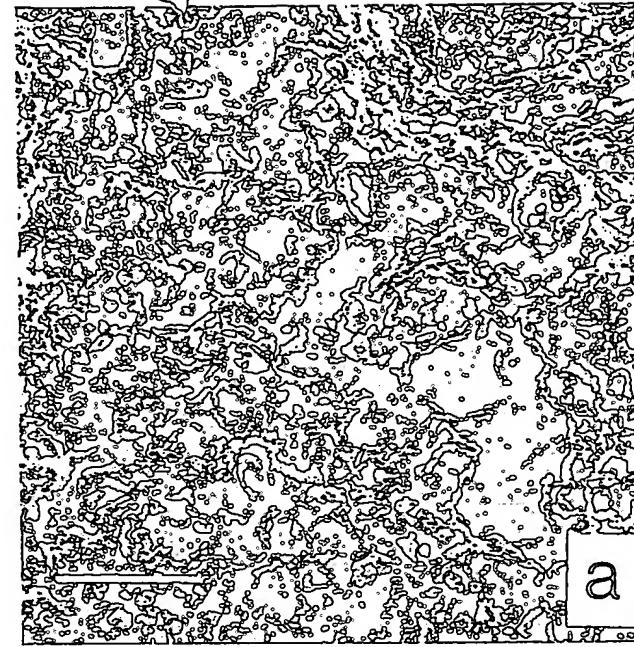


Fig. 6—SEM photomicrographs of the 24-hour CPC specimen. (a) Bar = 10.0 μm ; (b) bar = 0.1 μm .

action rate may be limited by factors that are basically unrelated to the amounts of the starting materials and the reaction products present in the system at any given time. Such factors could be related to the surface area of DCPA, which would dissolve more slowly than TTCP under acid and neutral pH conditions, or to the diffusion distances over which the calcium and phosphate ions must migrate in order to form OHAp. The change in compressive strength as a function of time (Fig. 1) followed a pattern essentially the same as that for the extent of reaction, and the strong correlation between the two (Fig. 3) clearly suggests that the formation of OHAp was responsible for the mechanical strength of the cement.

The mean compressive strength of 36 MPa for the 24-hour

specimens obtained in the present study is similar ($p > 0.1$) to the value of 34 MPa reported by Brown and Chow (1986) and significantly higher than the value of 21 MPa reported by Doi *et al.* (1987). Since in the study of Doi *et al.* (1987), DCPD instead of DCPA was used with TTCP, this might be a factor for the observed difference in the strength.

In previous studies, the CPC powder also contained OHAp seeds at a level from approximately 3 wt% (Brown and Chow, 1986; Sugawara *et al.*, 1990; Chow *et al.*, 1987) to 40 wt% (Takezawa *et al.*, 1987). OHAp was included in the mixture because it appeared to enhance the cement setting reaction so as to reduce the setting times and to increase the compressive strengths. The present study showed that a mixture which did not contain OHAp seeds was also capable of rapid setting and of yielding samples with compressive strengths comparable with those of the specimens formed from OHAp-seeded formulations. This, however, does not imply that OHAp seeds would not have advantageous effects had OHAp been incorporated into the mixture in the present study. The data obtained in the present study may, in fact, serve as a baseline for further studies on the effects of OHAp seeds on strengths.

CPC is a relatively simple material formed by combining a calcium phosphate mixture with an aqueous solution. On the other hand, based on the chemistry of the cement setting reaction, it would seem that the properties of CPC, *e.g.*, setting times, compressive and tensile strengths of the set cement, porosity, solubility, etc., may be affected by a rather large number of parameters. These include: (1) use of either DCPA or DCPD with TTCP in the solid phase; (2) particle sizes of TTCP and DCPA (DCPD); (3) inclusion of F in soluble (NaF) and sparingly soluble (calcium fluoride) forms in the solid; (4) inclusion of OHAp seeds and properties, *e.g.*, particle size, surface area, etc., of the seeds; (5) use of water, a dilute acid, or other aqueous liquid (serum, blood, etc.) as the liquid phase; and (6) inclusion of F, background electrolytes, and other additives in the liquid.

In its present state, CPC does not compare favorably with currently available dental cements in terms of setting time and strength. On the other hand, CPC has the unique advantage that its composition is nearly identical to that of tooth and bone mineral. Its high biocompatibility would make the material useful in applications where the cement is in contact with vital tissues. Compared with currently available calcium phosphate biomaterials, CPC is the only material that can be used in a paste form, is self-setting, and forms a pure OHAp. Further studies are warranted so that cement properties may be improved to meet requirements for various applications.

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